Continued Examination under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 6, 2011 has been entered.

Claim Status

2. This action is in response to papers filed on January, 2011. Claims 1-19, 21-25 and 27-35 are pending in this application. Claim 1 is amended and new claim 35 is added. The claim amendments have been reviewed and entered. Applicant's arguments filed January 6, 2011 have been fully considered and addressed following the claim rejections.

3. Claims 8-16 and 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and Applicant's timely traversed election requirement made final on June 12, 2007.

4. Claims 1-7, 17, 19, 21-25 and 27-35 are under examination.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-7, 17, 28-30 and 32 are rejected under 35 U.S.C. 102(e) as being anticipated by Peeters (USPN 6,762,056 issued Jul. 13, 2004, effective filing date May 16, 2001).

The claimed invention is drawn to a molecular detection method for visualizing and identifying an individual chain molecule uprightly disposed relative to the plastic substrate surface by probing with a scanning probe microscope in solution. As discussed below Peeters teaches detecting individual protein molecule on the plastic substrate surface using an atomic force microscope in solution.

Regarding claim 1, Peeters teaches a molecular detection method comprising a substrate 1, wherein surface is coated with coating 2 having random topology further comprising adsorption sites 10 for binding a protein containing columns 5, bumps 3, ridges, and spikes 4, which are uprightly disposed relative to the substrate surface (Fig. 1, column 9, lines 52-63, column 10, lines 4-12) and further teaches that the substrate surface comprises plastic substrate surface (column 15, lines 43-49). It is noted that the

open claim language "comprising" can include other material on the surface such as coating on the plastic surface taught by Peeters.

Also, the MPEP 2111.03 makes it clear that the transitional term "comprising" is open-ended and does not exclude additional, unrecited elements (See, e.g., > Mars Inc. v. H.J. Heinz Co., 377 F.3d 1369,1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004). Also the term "comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim (Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997). In the instant case, Peeters teaches the plastic substrate surface, which meets the limitation of the substrate of claim 1.

Peeters also teaches that a protein 15 is adsorbed (i.e., immobilized) on the adsorption site 10 having topology complementary to column, ridges and spikes uprightly disposed relative to the surface (Fig. 2 and column 10, lines 17-34). The protein 15 of Peeters is the individual chain molecule as recited in the instant claim 3.

Peeters also teaches the visualizing and identifying the a protein molecule (i.e., individual chain molecule) immobilized on the substrate surface by probing with the atomic force microscope (AFM), or scanning tunneling microscope (STM) in solution (i.e., fluid covering the test surface) so as to observe a profile of the substrate surface having individual protein molecule 15 immobilized thereon (Fig. 3 and column 8, lines 8-17, column 10, lines 35-65 and column 13, lines 31-54). The AFM and the STM of Peeters are the scanning probe microscopes as recited in the instant specification (USPGPUB paragraph 0075).

With respect to the new limitation of probing with a scanning probe microscope in a solution, which is a an aqueous solution containing a salt or a buffer solution, Peeters explicitly teaches the step of probing with a scanning probe microscope in a buffer solution (column 19, lines 37-54 and column 20, lines 1-32). The teachings of Peeters in column 19, lines 37-48 regarding the new limitation is listed below for Applicant's convenience.

> In another embodiment of the methods provided herein, the test surface is positioned in a fluidics cell within an AFM, with fluidic inlets and outlets that permit solutions and washing agents to be reacted with the test surface without having to move the surface or repositioning the AFM tip. A fluidics cell may be a simple walled structure, such as a rubber or metal-plus-rubber ring, that is positioned on top of the test, surface so the area to be examined is contained within the walls so as to hold a small amount of liquid on top of the test area. The fluidics cell is sufficiently large in diameter so the AFM sensor can fit into it and scan the test surface (Emphasis is underlined by the Examiner).

Regarding claim 2, as described above in the rejection of claim 1, Peeters teaches that the protein molecule 15 immobilized on the plastic substrate surface 1 having topology complementary to column, ridges and spikes uprightly disposed relative to the surface (Fig. 2 and column 10, lines 17-34) and is the uprightly disposed single strand molecule as recited in the instant claim 3.

Regarding claim 3, Peeters teaches a protein molecule uprightly disposed on the substrate (Fig. 2 and column 10, lines 17-22) and is the uprightly disposed single strand molecule as recited in the instant claim.

Regarding claim 4, Peeters teaches that the protein chain molecule immobilized on the substrate surface 1 in upright position (i.e., single strand molecule) forms a

complex with antibody molecule (column 16, lines 42-64), thus teaching surface is multiple strand molecule formed by protein and an antibody.

Regarding claim 5, Peeters teaches that the multiple strand molecules are a complex of a protein and an antibody (column 16, lines 42-43).

Regarding claim 6, Peeters teaches mapping and measuring the number of adsorption sites occupied by the protein on the surface area of the substrate (Figs. 5 and 6 and column 11, lines 49-67 and column 12, lines 1-23), which encompasses detecting g a molecule comprises counting the number of detected protein chain molecules per unit area.

Regarding claim 7, Peeters teaches mapping and measuring the number of adsorption sites occupied by the protein on the surface area of the substrate to obtain molecular localization information of the protein molecule on the substrate surface (Figs. 5 and 6 and column 11, lines 49-67 and column 12, lines 1-23).

Regarding claim 17, Peeters teaches a production process for a substrate with a chain molecule immobilized thereon, the production process as recited in claim 1 (Figs. 1 and 2 and column 9, lines 52-67 and column 10, lines 1-34).

Regarding claim 28, Peeters teaches that the substrate 1, wherein surface is coated with coating 2 having random topology further comprising adsorption sites 10 for binding a protein containing columns 5, bumps 3, ridges, and spikes 4, which are uprightly disposed relative to the substrate surface, which are substantially perpendicular to from the substrate surface (Fig. 1, column 9, lines 52-63, column 10, lines 4-12) and further teaches the substrate is a plastic (column 15, lines 42-47).

Regarding claim 29, Peeters teaches that the profile is observed using atomic force acting between the substrate surface having the individual protein chain molecules immobilized thereon and a probe of the AFM (Fig. 3 and column 9, lines 34-38 and column 10, lines 46-55).

Regarding claim 30, Peeters teaches that the profile is observed using AFM and further teaches that the AFM detects atomic scale features based on the force or the atomic interactions between the features present against a very fine tip of the AFM on the microcantilever, which measures the interaction by measuring an amount of flexing of the probe caused by the force between feature on the surface and the probe (column 9, lines 34-51).

Regarding claim 32, Peeters teaches a protein chip (column 23, line 34).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-7, 17, 19, 21-25 and 27-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (Nano Letters, 2002, 2, 863-867) in view of Obremski et al (USPGPUB 2002/0001853 published Jan. 3, 2002) and further in view of Henderson-2 et al (USPGPUB 2002/0042081 published Apr. 11, 2002).

Regarding claim 1, Liu teaches a molecular detection method comprising visualizing and identifying chain molecule (Figs. 4A and 4G, pg. 865, column 2, paragraph 3) immobilized on a substrate and immobilized being uprightly disposed relative to said substrate (Fig. 1, pg. 865, column 1, paragraph 1, pg. 866, column 2, paragraph 1, lines 3-6) by probing with scanning probe microscope in solution so as to observe profile of the chain molecules immobilized on the substrate surface (Abstract, Figs. 3A and 4A, pg. 865, column 2, paragraph 2).

With respect to the new limitation of probing with a scanning probe microscope in a solution, which is a an aqueous solution containing a salt or a buffer solution, Liu teaches probing with a scanning probe microscope in a buffer solution (pg. 865, column 2, paragraph 2).Liu does not teach a plastic substrate and visualizing and identifying an individual chain molecule on the plastic substrate surface.

Regarding claim 2, Liu teaches that chain molecule (i.e., single stranded DNA) is immobilized on the gold surface (Fig. 2C, pg. 864, column 1, and last paragraph) and is

an uprightly disposed single stranded DNA molecule (i.e., stand up configuration, pg.865, column 1, paragraph 1).

Regarding claim 3, Liu teaches that the uprightly single strand molecule is a nucleic acid (Fig. 1, pg. 865, column 1, and paragraph 1).

Regarding claim 4, Liu teaches that the chain molecule is in stand up position (Fig. 1, pg. 865, column 1, paragraph 1) and the binding of DNase I molecule to the uprightly disposed chain molecule comprises multi-strand molecule.

Regarding claim 5, Liu teaches that the multiple strand molecules are a complex of single strand DNA and protein DNase I (pg. 865, column 2, paragraphs 2 and 3, pg. 866, column 1, paragraph 1).

Regarding claims 6 and 7, Liu teaches the imaging of single strand DNA on the substrate surface (i.e., visualizing) and further teaches that the 80.5 nm2 area contains 26 molecules (Fig. 3E, lane a2, area indicated by an arrow, pg. 865, column 1 and paragraph 2), thus teaching counting the number of detected nucleic acid molecules (i.e., chain molecules) per unit area (limitation of claim 6). Liu also teaches that number of nucleic acid molecules identifies the smallest DNA dot on the substrate surface (pg. 865, column 1, paragraph 2), which encompasses giving molecular localization information (limitation of claim 7).

Regarding claim 17, Liu teaches a production process for immobilizing the single stranded DNA, i.e., chain molecule on a substrate (Fig. 2, substrate – labeled as Au (III), pg. 864, column 1, paragraph 4) and further teaches that the immobilized single strand DNA is in uprightly disposed position (Fig. 1, pg. 865, column 1, paragraph 1).

Regarding claim 19, Liu teaches a molecular detection method comprising visualizing and identifying chain molecule (Figs. 4A and 4G, pg. 865, column 2, paragraph 3) immobilized on a substrate and as immobilized being uprightly disposed relative to the substrate so as to observe a profile of the substrate surface having chain molecule immobilized there on (Figs. 1 and 4C, pg. 865, column 1, paragraph 1) by probing with scanning probe microscope in solution (Abstract, Figs. 3A and 4A, pg. 865, column 2, paragraph 2), wherein the molecule immobilized on the substrate is a nucleic acid (Fig. 2, pg. 864, column 1, paragraph 3). Liu do not teach the plastic substrate and visualizing and identifying an individual chain molecule on the plastic substrate surface.

Regarding claim 21, Liu teaches that the chain molecule is in stand up position (Fig. 1, pg. 865, column 1, paragraph 1) and the binding of DNase I molecule to the uprightly disposed chain molecule comprises multi-strand molecule.

Regarding claim 22, Liu teaches that the multiple strand molecules are a complex of single strand DNA and protein DNase I (pg. 865, column 2, paragraphs 2 and 3, pg. 866, column 1, paragraph 1).

Regarding claims 23 and 24, Liu teaches the imaging of single strand DNA on the substrate surface (i.e., visualizing) and further teaches that the 80.5 nm2 area contains 26 molecules (Fig. 3E, lane a2, area indicated by an arrow, pg. 865, column 1 and paragraph 2), thus teaching counting the number of detected nucleic acid molecules (i.e., chain molecules) per unit area (limitation of claim 23). Liu also teaches that number of nucleic acid molecules identifies the smallest DNA dot on the substrate

surface (pg. 865, column 1, paragraph 2), which encompasses giving molecular localization information (limitation of claim 24).

Regarding claim 25, Liu teaches a production process for immobilizing the single stranded DNA, i.e., chain molecule on a substrate (Fig. 2, substrate – labeled as Au (III), pg. 864, column 1, paragraph 4) and further teaches that the immobilized single strand DNA is in uprightly disposed position (Fig. 1, pg. 865, column 1, paragraph 1).

Regarding claims 27 and 28, Liu teaches that the molecule, as immobilized, is uprightly disposed relative to the substrate so as to extend substantially perpendicularly from said substrate surface (Figs. 1 and 3A, pg. 865, column 1, paragraph 1, lines 2-4).

Regarding claims 29 and 33, Liu teaches that the profile is observed using frictional force acting between the substrate surface having the individual chain molecules immobilized thereon and a probe of the scanning probe microscope (Compare the profile Fig. 4C versus 4H and pg. 866, column 1, paragraph 1). Liu also teaches the interaction between the methyl group and the AFM tip corresponds to a frictional force (pg. 866, column 1, paragraph 1, lines 23-28), which is reasonably interpreted as atomic force in view of lack of limiting definition for "atomic force" in the instant specification.

Regarding claims 30 and 34, Liu teaches that the profile is observed by measuring an amount of single stranded DNA left after the DNase I digestion caused by interaction between said DNA and DNase I (paragraphs 0051-0054). The force required to digest single strand DNA by DNase I of Liu is reasonably interpreted as atomic force in view of lack of limiting definition for "atomic force" in the instant specification.

Regarding claim 31, Liu teaches that the substrate having a chain molecule immobilized there on is a DNA chip (Fig. 2C)

Regarding claim 32, Liu teaches selective immobilization of proteins on the substrate surface (pg. 863, column 2, paragraph 1, lines 15-19) and is protein chip as recited in the instant specification (USPGPUB paragraph 0063).

Regarding claim 35, Liu teaches the solution is a buffer solution (pg. 865, column 2, paragraph 2).

As discussed above, regarding claims 1 and 19, Liu does not teach that the substrate is a plastic substrate. However, a plastic substrate for immobilizing chain molecules was known in the art at the time the claimed invention was made as taught by Obremski

Obremski teaches an assay method comprising a plastic substrate (paragraph 0038) for immobilizing oligonucleotide probe (paragraph 0010). Obremski also teaches that the molecules immobilized on the plastic substrate stand up "vertically" from the surface (paragraph 0071). Obremski also teaches that the plastic surface is optically transparent, has a higher refractive index than water, easy to configure to different dimensions and amenable for chemical coupling and is well suited for molecular detection by AFM and evanescent wave excitation method (paragraphs 0038 and 0071), thus providing the motivation for using the plastic substrate for immobilizing the nucleic acid probe of Liu.

As discussed above, Liu teaches a method comprising gold surface to immobilize the DNA molecule in upright position suitable for AFM scanning. Obremski teaches

immobilizing the molecules vertically (i.e., in upright position) on a plastic substrate and further teaches the advantages of using the plastic substrate for immobilizing the DNA for AFM scanning. Since both gold and plastic substrates are compatible for AFM scanning, use of plastic substrate for immobilizing individual chain molecule is obvious over Liu and Obremski.

It would have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the substrate of Liu with the plastic substrate of Obremski et al with a reasonable expectation of success with the expected benefit of having a plastic surface, that is optically transparent, easy to configure to different dimensions and amenable for chemical coupling and is well suited for molecular detection by AFM and evanescent wave excitation as taught by Obremski (paragraphs 0038 and 0071).

Regarding claims 1 and 19, Liu teaches the visualizing and calculating about 26 molecules in an 80.5 nm2 area (Fig. 3E, lane a2, area indicated by an arrow, pg. 865, column 1 and paragraph 2). Obremski also teaches an AFM scanning of immobilized avidin array and further teaches that avidin extends 200 nm vertically from the surface and binds to biotin (paragraph 0071). Liu and Obremski do not teach visualizing and identifying an individual chain molecule by scanning probe microscope. However, visualizing and identifying an individual chain molecule by scanning probe microscope was known in the art at the time the claimed invention was made as taught by Henderson-2.

Henderson-2 teaches a method for detecting molecular interaction between an object and a surface comprising the steps of affixing the a plurality of object 12 on the substrate surface 10 (viz., Fig. 4a) and detecting the location and size of the object 12 by scanning the entire surface image using AFM in solution (Fig. 1b and Example 1 and paragraphs 0037- 0038, 0041 and 0046). Henderson-2 also teaches that the substrate comprises polystyrene (paragraph 0066), which is a plastic as defined by Obremski (paragraph 0038). Henderson-2 also teaches that the "utilization of an AFM to run a scan is well known to those skilled in the art and enables the user to determine the location of the objects on the surface" (paragraph 0038). Henderson-2 further teaches that the object 12 further comprises a first object and a second object bound together on the surface consists of nucleic acid and a complementary nucleic acid (paragraph 0046). Henderson-2 also teaches locating the objects using AFM and characterizing the force necessary for separating the first and second objects based on the AFM probe deflection (paragraphs 0043-0046), which also encompasses visualizing individual objects. The combined teaching of detecting the location and size of an object (i.e., nucleic acid molecule on the substrate surface) of Henderson-2 encompasses visualizing (i.e., imaging) and detecting (i.e., size) of an individual molecule (i.e., object). Henderson-2 also teaches that the AFM imaging allows for rapid and inexpensive screening of large number of binding interactions for categorizing and characterizing the binding affinity between two interacting molecules (paragraph 0021).

As described above, Liu teaches imaging of nucleic acids using AFM in solution. Henderson-2 teaches a method step of imaging the surface (i.e., visualizing) and

detecting (i.e., identifying) surface bound molecules using AFM in solution for rapid and inexpensive way screening for molecular interactions between two binding partners including nucleic acids (paragraphs 0021 and 0046), thus providing a motivation f to include the visualization and identification of individual molecules by AFM of Henderson-2 in the method of Liu. Henderson-2 further teaches that the AFM scanning in solution is also routinely practiced in the art and one having the skill in the art able to locate and identify molecules on the surface (paragraph 0038). Therefore claimed method steps of visualizing, identifying an individual chain molecules on a plastic substrate are obvious over Liu, Obremski and Henderson-2.

It would have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the visualizing and identifying step of Liu with the method of step visualizing and identifying individual object on the surface of Henderson-2 with a reasonable expectation of success with the expected benefit of a rapid and inexpensive screening of large number of binding interactions for categorizing and characterizing the binding affinity between two nucleic acid molecules as taught by Henderson-2 (paragraph 0021). The teachings of Henderson et al would be beneficial to Liu for properly selecting nucleic acid probes for the fabrication of DNA biosensors, biochips and engineering of biostructures as desired by Liu (pg. 866, column 2 and paragraph 1).

Response to Remarks from the Applicant

10. Applicant's remarks have been fully considered (Remarks, pgs. 9-25). It is noted that Applicant makes general statements that the cited arts of Peeters, Liu, Obremski and Henderson-2 do not teach the method steps of claims 1-7,17, 19, 21-25 and 27-35 (Remarks, pgs. 9-13). Applicant also repeats the arguments regarding the rejections made over cited references (Remarks, pgs. 13-25). Applicant also points out the novelty of the claimed invention (Remarks, pgs. 14 and 15). However, as discussed below the novelty of the claimed invention is either anticipated or obvious over cited references. Also, the redundant arguments made by the Applicant are addressed together as discussed below.

It is maintained that the method steps of claims 1-7, 17, 28-30 and 32 are being anticipated by Peeters and claim 1-7, 17, 19, 21-25 and 27-35 are being obvious over Liu in view of Obremski and further tin view of Henderson-2.

11. Applicant's arguments filed on January 6, 2011 with respect to claims 1-7, 17, 28-30 and 32 as being anticipated by Peeters have been fully considered (Remarks, pgs. 15 and 16) and are not persuasive because of the following reasons.

Applicant argues that Peeters does not disclose, nor would have suggested, probing with a scanning probe microscope in a solution which is an aqueous solution containing a salt or a buffer solution, as in claim 1 and all claims dependent thereon, and as in claim 35 (Remarks, pg. 12, paragraph 2) and further argues that Peeters removes the solution with unadsorbed protein molecules from the test surface. It is

respectfully submitted that this reference would have neither disclosed nor would have suggested, and in fact would have taught away from, probing with the scanning probe microscope in the solution, particularly wherein such solution is an aqueous solution containing a salt, or a buffer solution (Remarks, pg. 16, paragraph 12).

Applicant is reminded that claim 35 is not rejected either being anticipated by or being obvious over Peeters.

These arguments regarding Peeters not teaching the method steps of claim 1 are not persuasive because Peeters explicitly teaches the step of probing with a scanning probe microscope in a buffer solution (column 19, lines 37-54 and column 20, lines 1-32). The teachings of Peeters in column 19, lines 37-48 regarding the new limitation is listed below for convenience.

> In another embodiment of the methods provided herein, the test surface is positioned in a fluidics cell within an AFM, with fluidic inlets and outlets that permit solutions and washing agents to be reacted with the test surface without having to move the surface or repositioning the AFM tip. A fluidics cell may be a simple walled structure, such as a rubber or metal-plus-rubber ring, that is positioned on top of the test, surface so the area to be examined is contained within the walls so as to hold a small amount of liquid on top of the test area. The fluidics cell is sufficiently large in diameter so the AFM sensor can fit into it and scan the test surface (Emphasis is underlined by the Examiner).

The teaching of buffer solution for AFM scanning by Peeters is listed below (column 20, lines 8-18).

> After the test surface tovology has been measured, the sample with the protein solution-is introduced to the lo fluidics cell through the inlet port. The protein is permitted to react with the test surface for a period of time, then it is removed from the test surface by draining the protein solution from the outlet while introducing a washing fluid, such a buffer of specified pH and ionic strength, through the inlet. Following washing, the AFM again scans the test surface within its field of regard to identify adsorbed proteins by comparing the surface topology measurements to the topology measurements in the database. (Emphasis is underlined by the Examiner).

The citations clearly illustrates that the liquid (i.e., the buffer, e.g., see column 20, lines 1-32) is on the test surface while AFM sensor (i.e., scanning probe microscope) scans the surface. It is also noted that Peeters teaches a plurality of embodiments wherein in some specific embodiments the scanning of the surface is done by removing the solution. However, as cited above, Peeters explicitly teaches probing with a scanning probe microscope in a buffer solution and therefore arguments regarding Peeters not teaching the buffer solution from the claimed invention are not persuasive.

Applicant further asserts that Peeters removes the solution with unadsorbed protein molecules from the test surface. It is respectfully submitted that this reference would have neither disclosed nor would have suggested, and in fact would have taught away from, probing with the scanning probe microscope in the solution, particularly wherein such solution is an aqueous solution containing a salt, or a buffer solution (Remarks, pg. 16, paragraph 2). These arguments are not persuasive because as discussed above, the Examiner acknowledges that Peeters teaches a plurality of embodiments wherein in some specific embodiments the scanning of the surface is done by removing the solution. However, as cited above, Peeters explicitly teaches probing with a scanning probe microscope in a buffer solution and therefore arguments regarding Peeters teaching away from probing with the scanning probe microscope in the buffer solution are not persuasive.

12. Applicant's arguments filed on January 6, 2011 with respect to claims 1-5, 17, 19, 21, 22 and 25-34 rejected under 35 USC 103(a) as being obvious over Liu, Obremski

and Henderson-2 have been fully considered (Remarks, pgs. 16-21) and are not persuasive for the following reasons.

It is noted that Applicant reiterates the arguments made previously regarding the teachings of Liu that one of ordinary skill in the art need not observe the molecules individually so as to produce the nanopatterns consisting of DNA molecules (Remarks, pg. 17, paragraph 3). Applicants further assert that Liu would not suggest "molecular detection methods" and visualizes and identifies the aggregates of the thiolated ssDNA molecules (Remarks, pg. 18, paragraph 1). These arguments have been addressed before and are not persuasive for the reasons of the record.

Applicant is also reminded that claim 1 is rejected over Liu in view of Obremski and Henderson-2. Applicant's arguments are directed to attacking the references individually, which are not persuasive because claim 1 is rejected over Liu, in view of Obremski and further in view of Henderson-2. Also courts have ruled that arguments regarding the obvious rejection by attacking references individually are not persuasive where the rejections are based on combinations of references (See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, as discussed in section 9, Liu teaches the method steps including the step of probing with the scanning probe microscope in the buffer solution. Liu does not teach that the DNA molecules are immobilized on the plastic substrate, which is taught by Obremski with motivation and the step of visualizing and identifying an individual chain molecule on the plastic substrate surface, which is

taught by Henderson-2 with motivation. For these reasons, arguments are not persuasive.

Applicant further argues that Liu's reference would have neither disclosed nor would have suggested such a molecular detection method as in the present claims, including the visualizing and identifying of an individual chain molecule immobilized on a plastic substrate surface and (while immobilized) uprightly disposed relative to the substrate surface, with the visualizing and identifying being performed by probing with a scanning probe microscope in solution, so as to make the observation of the profile of the substrate surface having the individual chain molecules thereon and observe the individual chain molecule immobilized uprightly on the plastic substrate surface (Remarks, pg. 17, last paragraph and pg. 18, first paragraph).

These arguments are not persuasive because claim 1 is rejected over Liu, Obremski and Henderson-2 and Examiner has acknowledged that Liu does not teach the DNNA molecules are immobilized on the plastic substrate, which is taught by Obremski and Henderson-2 teaches visualizing and identifying an individual chain molecule by scanning probe microscope.

Applicant further argues that the secondary references applied by the Examiner together with Liu would not have rectified the deficiencies thereof, such that the presently claimed invention as a whole would have been obvious to one of ordinary skill in the art (Remarks, pg. 18, paragraph 2).

These arguments are not persuasive because as discussed above in section 9, Obremski provides motivation for using the plastic substrate and Henderson-2 provides

motivation for visualizing and identifying an individual chain molecule by scanning probe microscope as discussed below.

With respect to the argument made by the Applicant regarding the teachings of Obremski, it is noted that Obremski teaches a plurality of embodiments and the Applicant citation of Obremski is unrelated to the plastic substrate (Remarks, pg. 19, paragraph 3). The teachings of Obremski with respect to the plastic substrate for molecular detection as discussed in section 9 are copied below.

> Obremski teaches an assay method comprising a plastic substrate (paragraph 0038) for immobilizing oligonucleotide probe (paragraph 0010). Obremski also teaches that the molecules immobilized on the plastic substrate stand up "vertically" from the surface (paragraph 0071). Obremski also teaches that the plastic surface is optically transparent, has a higher refractive index than water, easy to configure to different dimensions and amenable for chemical coupling and is well suited for molecular detection by AFM and evanescent wave excitation method (paragraphs 0038 and 0071), thus providing the motivation for using the plastic substrate for immobilizing the nucleic acid probe of Liu.

Both Liu and Obremski teaches that the nucleic acid molecule immobilized on the substrate stand up vertically and suitable for molecular detection by AFM and therefore method steps are combinable.

Applicant further argues that Even assuming, arguendo, that the teachings of Obremski, et al. were properly combinable with the teachings of Liu, et al., such combined teachings would have neither disclosed nor would have suggested the presently claimed invention, including visualizing and identifying an individual chain molecule, immobilized on the substrate (and, while immobilized, being uprightly disposed relative to the substrate), by probing with a scanning probe microscope in solution (e.g., which is an aqueous solution containing a salt or a buffer solution) so as

to observe a profile of the surface of the substrate having the individual chain molecules immobilized thereon and observe the individual chain molecule immobilized uprightly on the plastic substrate surface, especially wherein the chain molecule is a nucleic acid; or the other features of the present invention as discussed previously, and advantages thereof (Remarks, pg. 19, paragraph 2).

These arguments are not persuasive because visualizing and identifying an individual chain molecule by scanning probe microscope is taught by Henderson-2.

With respect to the teachings of Henderson-2, Applicant emphasizes Henderson-2 discloses removal of objects for determining binding affinities. It is respectfully submitted that one of ordinary skill in the art concerned with in Liu, et al., producing nanostructures of DNA on surfaces, would not have looked to the teachings of Henderson-2, et al (Remarks, pg. 20, paragraph 2). These arguments are not persuasive because in paragraph 0029, Henderson-2 teaches

In the present invention description, the term "object" is utilized
to include any material that can be bound to a surface and detected
and/or removed using a probe, such as an AFM probe (Emphasis is underlined by the Examiner).

One having ordinary skill in the art would recognize that the teachings of object (i.e., nucleic acid) bound to the surface detected by AFM probe of Henderson-2 encompasses detecting the object on the surface and not removing the object from the surface. It is also noted that Henderson-2 teaches a plurality of embodiments. Applicant's arguments regarding the teachings of Henderson-2 of using AFM to remove the object from the substrate in one embodiment is acknowledged by the Examiner. However, it is emphasized that Henderson-2 also teaches the detection of object bound

to the surface by AFM (e.g., Fig. 1b). Therefore Applicant's arguments of Henderson-2 teaching removal of objects from the surface are not persuasive.

As discussed above in section 9, Henderson-2 teaches a method for detecting molecular interaction between an object and a surface comprising the steps of affixing the a plurality of object 12 on the substrate surface 10 (viz., Fig. 4a) and detecting the location and size of the object 12 by scanning the entire surface image using AFM in solution (e.g. Fig. 1b and paragraph 0038).

Liu teaches imaging of nucleic acids using AFM in solution and visualizing at least 26 nucleic acid d molecules on the surface (Fig. 3E and pg. 865, column 1, paragraph 1).Henderson-2 teaches a method step of imaging the surface (i.e., visualizing) and detecting individual molecule by AFM (Fig. 1b) and further teaches identifying surface bound molecules using AFM in solution for rapid and inexpensive way screening for molecular interactions between two binding partners including nucleic acids (paragraphs 0021 and 0046), thus providing a motivation to include the visualization and identification of individual molecules by AFM of Henderson-2 in the method of Liu. Henderson-2 further teaches that the AFM scanning in solution is also routinely practiced in the art and one having the skill in the art able to locate and identify molecules on the surface (paragraph 0038). Therefore claimed method steps of visualizing, identifying an individual chain molecules on a plastic substrate are obvious over Liu, Obremski and Henderson-2.

Applicant further argues that Liu is concerned with aggregates, it is respectfully submitted that looking to individual chain molecules, based on the Examiner's

characterization of Henderson-2, et al., would destroy Liu, et al. for its intended purpose. Thus, this modification of Liu, et al. is improper. See In re Ratti, 123 USPQ 349 (CCPA 1959). Moreover, Applicants respectfully traverse the Examiner's characterization of the teachings of Henderson-2, et al., again emphasizing that this reference is directed to removal of objects from a surface using a probe (Remarks, pg. 20,paragraph 3). These arguments are not persuasive, because Liu does not teach aggregates, but rather teaches detecting nucleic acid molecules on the surface of the substrate with AFM (Fig. 3E) and Henderson-2 teaches detecting single molecules on the surface of the substrate. Therefore teaching of single molecules by AFM on the surface by Henderson-2 would not destroy the nucleic acid molecules of Liu. For these reasons arguments are not persuasive.

Applicant's remaining arguments regarding Henderson-2 disclosing the removal of an object are repetitive (Remarks, pg. 20, paragraphs 2 and 4) and they are not persuasive for the reasons as discussed above.

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Narayan K. Bhat whose telephone number is (571)-272-5540. The examiner can normally be reached on 8.30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571)-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Narayan K. Bhat/

Examiner, Art Unit 1634

/Stephen Kapushoc/
Primary Examiner, Art Unit 1634